Plasma Concentrations of Thioridazine Metabolites and ECG Abnormalities

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Abstract □ Five acute schizophrenic patients were given a standard thioridazine dose (4 mg/kg/day po). Their plasma concentrations of thioridazine and its metabolites were determined by GLC, and their ECG's were recorded routinely. In four of the five patients, abnormal ECG's (malformation of the T-wave or lengthening of the repolarization time) were found whenever plasma concentrations of the thioridazine ring sulfoxide were elevated. No relationship could be detected between the appearance of ECG abnormalities and the concentrations of thioridazine and its other metabolites.

Keyphrases □ Thioridazine and metabolites—plasma concentrations and ECG abnormalities, relationship evaluated, humans □ ECG abnormalites—relationship to plasma concentrations of thioridazine and metabolites evaluated, humans □ Tranquilizers—thioridazine and metabolites, plasma concentrations and ECG abnormalities, relationship evaluated, humans

Abnormal electrocardiograms (ECG's) have been reported as an effect of thioridazine (1–6). This study explored the relationship of the plasma concentration of thioridazine and its metabolites during chronic thioridazine administration (4 mg/kg po) to the appearance of ECG abnormalities in schizophrenic patients. This investigation was one facet of ongoing studies on the pharmacokinetics of thioridazine (7) and mesoridazine (8) and clinical responses in acute schizophrenic patients.

EXPERIMENTAL

Subjects—The acute schizophrenic patients[1] selected were 21–55 years of age. None had a significant history of hepatic or cardiorenal disease, chronic alcoholism, or drug abuse. All subjects were drug free for at least 4 weeks prior to the study.

The selection of subjects was based on the independent diagnosis of schizophrenia by three psychiatrists. High scores on the major features of schizophrenia from three psychiatric rating scales, the Overall–Gorham brief psychiatric rating scale (9), the Hamilton depression rating scale (10), and the Wittenborn scale (10), and from an objective speech content analysis measure (11) corroborated the diagnosis of severe acute schizophrenia. Details of these methods for selecting subjects were reported previously (7).

Procedures—This was a placebo–drug, single oral dose, noncrossover study followed by daily drug administration. A liquid placebo was administered on Day 1. On Day 6, a single oral dose of thioridazine (4 mg/kg) was given. Starting on Day 10, thioridazine (4 mg/kg/day) was given in divided doses for 4–6 weeks. Generally, no neuroleptic other than thioridazine was administered to the patients.

Violent and unmanageable behavior, insomnia, or severe pain occasionally occurred in some subjects; these reactions were treated, when necessary, by supplementing the thioridazine with other medicaments. Specifically, chloral hydrate and meperidine were given to one patient and aspirin was given to another.

Blood was drawn for a drug screen and automated chemistry analysis[2] before thioridazine administration. On Day 6, blood was drawn for drug level determinations before and at 1, 4, 8, 24, 48, 72, and 96 hr after the initial oral thioridazine dose. After the 10th day, blood was drawn twice weekly for analysis.

Plasma thioridazine levels were measured by the GLC method of Dinovo *et al.* (12), which allows individual measurements for thioridazine and its metabolites.

ECG's, taken before and during drug administration, were read by members of the Cardiology Division, University of California Irvine Medical Center, having no knowledge of the nature of the study. The ECG's were reported to be abnormal if there was malformation of the T-wave or lengthening of the repolarization time. The morphology of the T-wave varied from blunting to inversion. The prolongation of repolarization appeared as a hypertrophy pattern, ST segment shifts, and abnormal QRST angles. Small Q-waves were reported as well as elevated ST segments. Occasionally, the ST segments became convex and U-waves appeared.

RESULTS AND DISCUSSION

Figures 1–5 show the variations in plasma levels of thioridazine and its metabolites following the continuous dose of thioridazine in five schizophrenic patients. The plasma level variations following the single dose of thioridazine on Day 6 are omitted in these figures and not considered in the results because no ECG abnormalities were noted for the 4 days following this single dose, probably because the plasma concentration of the metabolites of thioridazine did not reach sufficient levels for a necessary duration.

The fluctuations in plasma concentrations of thioridazine and its metabolites (mesoridazine, sulforidazine, and the thioridazine ring sulfoxide) can be accounted for on some occasions. Figure 1 (Patient C. K.) shows fluctuations in thioridazine, mesoridazine, and thioridazine ring sulfoxide plasma levels while the patient was receiving oral thioridazine at a dose of 4 mg/kg; some of these variations were possibly related to interruptions in the continuous oral administration of thioridazine. On the two occasions when abnormal ECG's were noted, the levels of thioridazine ring sulfoxide were close to 0.9 μg/ml; when normal ECG's were reported, the levels of thioridazine ring sulfoxide were lower, as were the levels of thioridazine and mesoridazine.

Figure 2 (Patient G. S.) also shows the plasma concentrations of thioridazine and its metabolites after the initiation on Day 10 of the continuous daily oral dosage of thioridazine (300 mg) at 4 mg/kg. The patient interrupted daily dosage of thioridazine on Days 25 and 39, and plasma measurements of drug level were not done between Days 22 and 29 and Days 36 and 43. ECG's were reported to be abnormal on two occasions when the plasma thioridazine ring sulfoxide levels were 1.4 μg/ml or above. Plasma thioridazine and mesoridazine concentrations were all below 0.6 μg/ml.

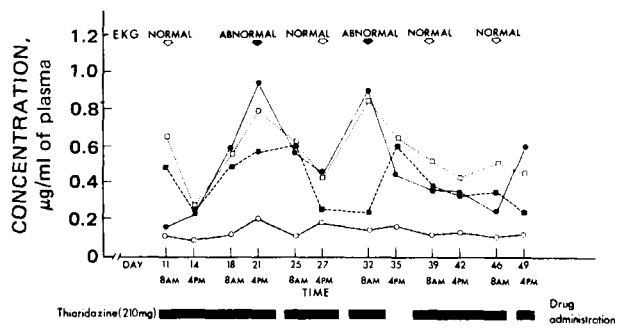

Figure 1—*GLC analysis of plasma concentrations of thioridazine and metabolites during standard daily oral dose (4 mg/kg) in Patient C. K. Key:* ■, *thioridazine;* □, *mesoridazine;* ○, *sulforidazine; and* ●, *thioridazine ring sulfoxide.*

[1] Adult Psychiatric Service, University of California Irvine Medical Center.
[2] SMA-6 and SMA-12.

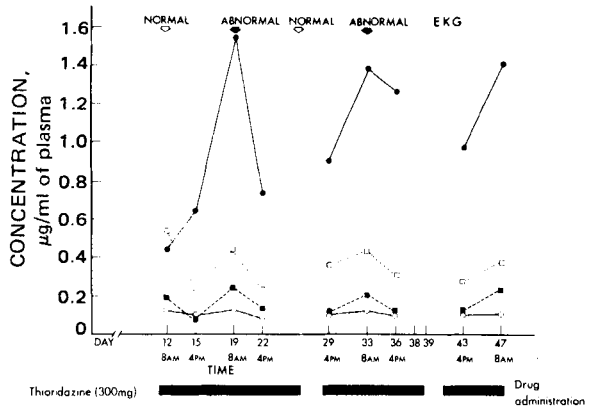

Figure 2—*GLC analysis of plasma concentrations of thioridazine and metabolites during standard daily oral dose (4 mg/kg) in Patient G. S. Key: ■, thioridazine; □, mesoridazine; ○, sulforidazine; and ●, thioridazine ring sulfoxide.*

Figure 3 (Patient R. R.) shows fairly steady-state plasma levels for thioridazine and its metabolites after Day 13 during the daily continuous oral dosage of 290 mg of thioridazine, except for Days 37–43 when there was a notable unexplained drop in plasma drug levels. On Days 22 and 34, abnormal ECG's were reported; the plasma levels of the thioridazine ring sulfoxide on these days were among the highest for this patient, namely, 2.2 μg/ml or above (the diagrammed levels for this metabolite are half the recorded value in Fig. 3).

With Patient S. C. (Fig. 4), continuous daily oral dosage of 300 mg of thioridazine was started on Day 10. Thioridazine, mesoridazine, and sulforidazine built up to a peak about Day 29, dropped off moderately about Day 33, and continued at a steady level until Day 50, except for the thioridazine ring sulfoxide which varied widely. These fluctuations are perhaps related to the activation of hepatic microsomal enzymes induced by the thioridazine and the other medication (chloral hydrate and meperidine) administered to this patient. Abnormal ECG's appeared when the plasma thioridazine ring sulfoxide levels exceeded 1.0 μg/ml.

Figure 5 (Patient H. D.) shows plasma drug concentrations after the patient was started on a continuous daily oral dose of 240 mg of thioridazine on Day 10. Although the thioridazine ring sulfoxide levels exceeded 1.0 μg/ml on several occasions, no abnormal ECG's were observed.

Of specific interest here are the relatively high plasma levels of the thioridazine ring sulfoxide and the fact that ECG changes were frequently, but not always, noted when these plasma levels reached or exceeded 0.9 μg/ml.

These findings suggest that the thioridazine ring sulfoxide metabolite of thioridazine induces ECG abnormalities in susceptible patients. The thioridazine ring sulfoxide was reported elsewhere[3] (13) to be pharmacologically inactive. The relationship of this metabolite to evidence of

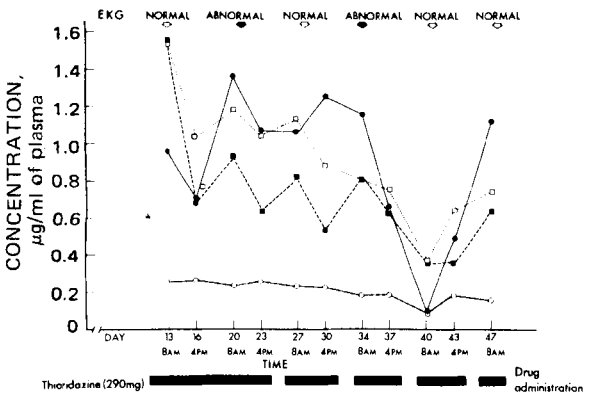

Figure 3—*GLC analysis of plasma concentrations of thioridazine and metabolites during standard daily oral dose (4 mg/kg) in Patient R. R. Key: ■, thioridazine; □, mesoridazine; ○, sulforidazine; and ●, thioridazine ring sulfoxide (half recorded level).*

[3] R. G. Muusze, unpublished Ph.D. dissertation, University of Amsterdam, Amsterdam, The Netherlands, 1975.

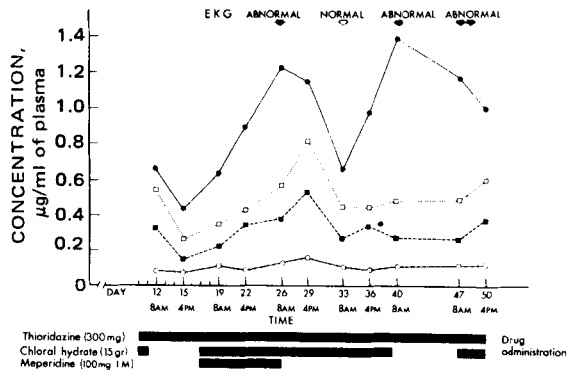

Figure 4—*GLC analysis of plasma concentrations of thioridazine and metabolites during standard oral dose (4 mg/kg) in Patient S. C. Key: ■, thioridazine; □, mesoridazine; ○, sulforidazine; and ●, thioridazine ring sulfoxide.*

interferences in myocardial conductance points to an interesting mechanism in the variety of biochemical pathways leading to a physiological adverse side effect.

If sufficient amounts of this metabolite had been readily available, the effects of the thioridazine ring sulfoxide on the heart in animals would have been studied. Unfortunately, only enough to serve as a standard in the GLC assays could be obtained. Therefore, it has not been possible to pursue the desirable definitive studies of the cardiotoxic effect of this specific metabolite.

The effect of thioridazine and its metabolites on the ECG has been reported essentially as changes in the T-wave morphology or interference with repolarization. The malformation of the T-wave can range from a simple apex blunting to broadening to notching to an actual inversion of the deflection (1, 2, 4). Investigation suggests that thioridazine treatment, alone or in combination with other phenothiazines or alcohol, may result in a lengthening of the time of repolarization to the extreme of ventricular arrhythmias, heart block, and death (2, 14–16). The abnormal repolarization category has included ECG patterns of hypertrophy, ST-segment shifts, abnormal QRST angles, and prolonged QT intervals.

The factors that bring about the ECG effects have not yet been clarified. Hypokalemia has been considered (3, 16), but deviations in serum electrolytes have not always been present (3, 17). The incidence of ECG T-wave abnormalities has been found to increase with the amount of thioridazine consumed per day (4, 18). The incidence of such abnormalities appears to be related to dose size, whereas the severity has been reported to be related to chronological age (4). The duration of treatment with thioridazine is not considered to be a factor in either the incidence or severity of these ECG changes (4).

Previous findings that dose size and chronological age are related to the incidence and/or severity of ECG abnormalities occurring with thioridazine are not inconsistent with the findings that high plasma concentrations of the thioridazine ring sulfoxide are frequently associated

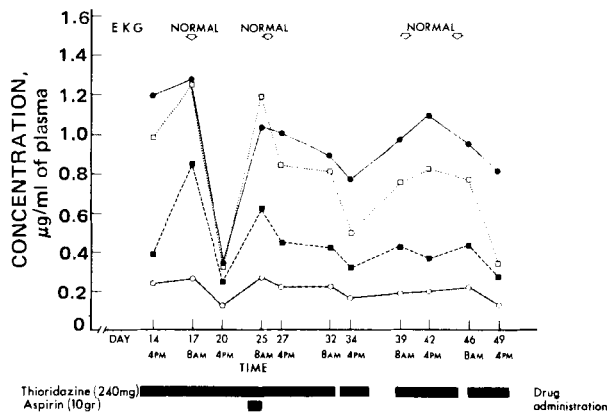

Figure 5—*GLC analysis of plasma concentrations of thioridazine and metabolites during standard daily oral dose (4 mg/kg) in Patient H. D. Key: ■, thioridazine; □, mesoridazine; ○, sulforidazine; and ●, thioridazine ring sulfoxide.*

with abnormal electroencephalographic changes. The pathogenic mechanism involved remains unknown, however, and it is hoped that this report will stimulate research in this area.

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Potential CNS Antitumor Agents—Phenothiazines II: Fluphenazine Analogs

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Abstract □ Fluphenazine was found to possess moderate, reproducible activity against the intraperitoneal L-1210 and P-388 leukemia murine tumor models. Seven ether derivatives of fluphenazine and eight compounds in which the terminal side-chain hydroxyl group was replaced by an amine function were prepared and evaluated in the intraperitoneal L-1210, P-388, and B16 melanoma systems as well as the intracerebral L-1210 and ependymoblastoma brain tumor models. While no substantial intracerebral activity was observed, seven derivatives possessed reproducible activity in the intraperitoneal L-1210 or P-388 system. Several gave T/C values of 150%. No B16 melanoma activity was observed. These compounds were also tested for their cytotoxic properties in culture against L-1210, P-388, and KB cells. The amine isosteres, while possessing little *in vivo* activity, were the most cytotoxic of the compounds prepared, with several having ED_{50} values <1 μg/ml.

Keyphrases □ Fluphenazine and various analogs—synthesized, CNS antitumor and cytotoxic activity evaluated □ Phenothiazines, various—synthesized, CNS antitumor and cytotoxic activity evaluated □ Antitumor activity, CNS—fluphenazine and various analogs evaluated □ Cytotoxic activity—fluphenazine and various analogs evaluated □ Structure-activity relationships—fluphenazine and various analogs evaluated for CNS antitumor and cytotoxic activity

Brain tumors and other cancers of the central nervous system (CNS) continue to constitute a difficult clinical problem. Approximately 8500 patients per year die from brain tumors. CNS cancer is the second most common type in children under 15 years old (1). Secondary CNS tumors are encountered among leukemia patients (2), who are often treated prophylactically with irradiation of the CNS or with intrathecal methotrexate administration (3, 4).

Drugs able to enter the CNS are obvious candidates as potential CNS antitumor agents. Psychotropic drugs in general (5–8) and phenothiazine derivatives in particular (5–20) have been investigated for their antitumor properties. The possibility that phenothiazine derivatives may have had a favorable effect on human carcinomas has been discussed (19).

Although some activity has been observed with phenothiazines in animal tumor models when the tumor was intraperitoneally or subcutaneously implanted, no CNS antitumor activity was found when an intracerebral tumor model was studied using phenothiazine nitrogen mustard derivatives (20). At the time the phenothiazine mustard investigation (20) was initiated, a second, parallel, attempt to produce a CNS antitumor agent based on a nonalkylating phenothiazine system was started. This work was based on the intraperitoneal murine leukemia activity observed during the initial testing of trifluoperazine (I), fluphenazine (II), and the hydroxyethyl ether of fluphenazine (III). Compounds I and II are known to penetrate the blood–brain barrier and to have significant CNS activity in humans. It appeared that if a compound of this type could be discovered that had high intraperitoneal